



SUBCLINICAL HYPOTHYROIDISM PREVALENCE AND SELENIUM LEVELS IN WOMEN OF NORTH KHORASAN, IRAN: A CROSS-SECTIONAL STUDY

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SUMMARY – Individuals with subclinical hypothyroidism have an increased risk of developing clinical hypothyroidism. The thyroid gland, which has the highest concentration of selenium per gram of tissue among adults, plays a crucial role in the metabolism of thyroid hormones. This study aimed to investigate the prevalence of subclinical hypothyroidism in the North Khorasan province of Iran and assess the serum selenium levels in affected individuals. We conducted a prospective study involving 550 females aged 20-55. Serum samples were collected from individuals based on the study's inclusion and exclusion criteria. We measured the serum levels of thyroid-stimulating hormone (TSH), thyroxine (T4), and triiodothyronine (T3). Subsequently, individuals with high TSH but normal T4 and T3 levels were selected for further analysis (group I). The serum levels of TSH, T4, T3 (using the ELISA method), and selenium (using the atomic absorption method) were measured and compared with those of a control group comprising healthy women matched to group I in terms of number, age, and body mass index. The overall prevalence of subclinical hypothyroidism in the study population was 6.48%. Significant differences were observed in serum TSH and selenium levels between the subclinical hypothyroidism group and the control group. Furthermore, a positive correlation between TSH and selenium levels was found exclusively within the subclinical hypothyroidism group. The occurrence of subclinical hypothyroidism was positively correlated with serum selenium levels.

Keywords: *Selenium; Thyroid hormones; Subclinical hypothyroidism*

Introduction

Thyroid gland disorders rank as the second most prevalent endocrine disorder, following diabetes

mellitus. These disorders directly impact the production of hormones by the thyroid gland. Subclinical hypothyroidism refers to an increased level of thyroid-stimulating hormone (TSH) alongside a normal level of free thyroxine (FT4). This condition is more prevalent among women and the elderly, making it essential to investigate its clinical significance due to its high prevalence (3-12%) in the general population¹⁻³. There is significant disagreement regarding the treatment of subclinical disorders. The recommended

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treatment for subclinical hypothyroidism is when the patient is pregnant, infertile, experiences symptoms, or is at risk of developing hypothyroidism⁴. In adults, the thyroid gland possesses the highest amount of selenium per gram of tissue⁵. Selenium levels in the body depend on population characteristics, diet, geographical location, and soil composition⁴. Selenium plays a crucial role in the thyroid gland by facilitating antioxidant function and the metabolism of thyroid hormones. Selenium (Se) is an essential element involved in various biological processes through selenoproteins, such as iodothyronine-deiodinase (DIO)^{6,7}. Among these selenoproteins, DIO1 and DIO2 are responsible for synthesizing the active form of thyroid hormone triiodothyronine (T3) from thyroxine (T4). Selenium deficiency may reduce the expression and/or activities of DIO1 and DIO2, thereby affecting T4 and T3 levels, respectively⁸.

Research has demonstrated that regions with sufficient selenium levels in the soil exhibit significantly lower prevalence rates of pathological thyroid diseases, including hypothyroidism, subclinical hypothyroidism, autoimmune thyroid diseases, and thyroid enlargement, compared to regions with selenium deficiency⁹.

In other words, decreased serum selenium levels in areas with low selenium levels in soil and agricultural products are associated with an increased risk of thyroid diseases, including subclinical hypothyroidism. The selenium content in soil varies based on geographical location, necessitating investigations into selenium's effects on diseases specific to each area¹⁰⁻¹². Based on previous studies in Iran, Golestan province has a higher level of selenium in the soil and the serum level of the residents of that region¹³.

Considering the critical role of this element in the function of the thyroid gland, and that no research has been done in this region, the current study was conducted with the aim of investigating the amount of serum selenium in people with subclinical hypothyroidism compared to healthy people in the North Khorasan province of Iran.

Methods

This prospective study was conducted in 2021 and 2022 on females aged 20-55 referred to the Imam Ali Hospital of Bojnurd. It was approved by the Ethics

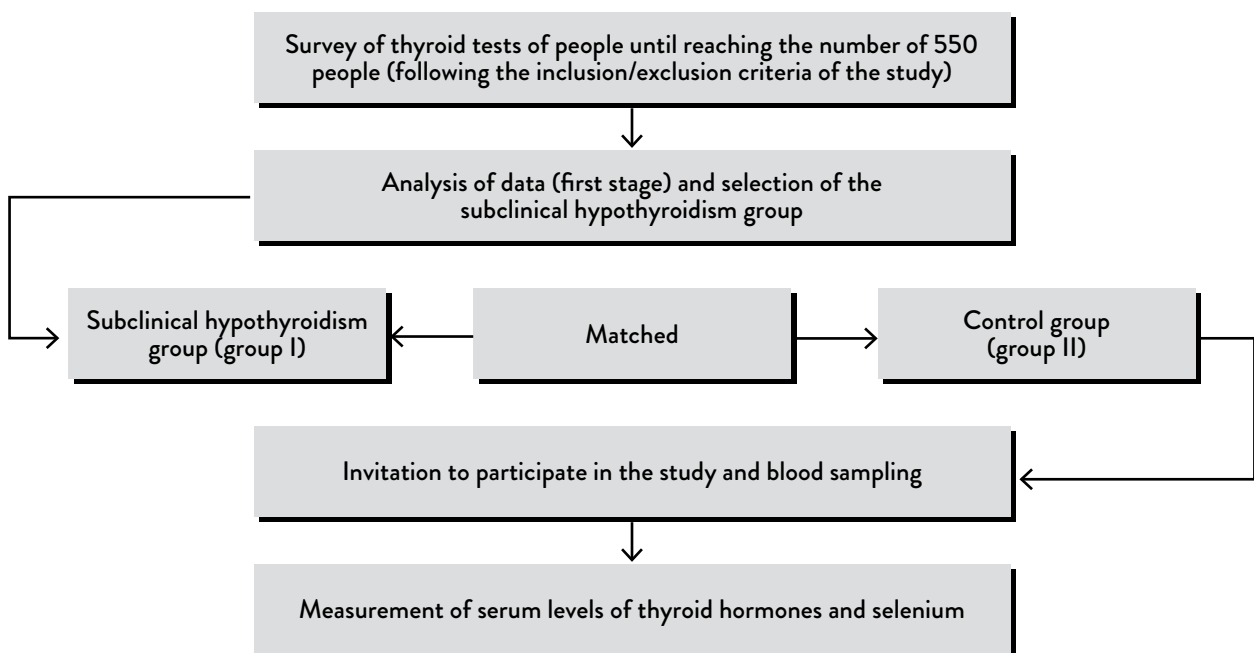


Figure 1. The method process

Committee of the North Khorasan University of Medical Sciences (IR.NKUMS.REC.1399.089). The sample size of 500 (95% confidence interval and α of 2%) was calculated based on a prevalence rate of 5.5% for subclinical hypothyroidism¹⁴, then increased to 550 (10%).

Exclusion criteria included the following: thyroid diseases or any known conditions that affect thyroid function or lipid metabolism, such as diabetes mellitus, kidney failure, nephrotic syndrome, pancreatitis, and pituitary/hypothalamic gland disorders.

Daily, we collected serum samples of individuals who met the inclusion/exclusion criteria of the study and stored them at -70°C .

After reaching the desired sample size (550 samples), TSH, T4, and T3 levels were measured by the ELISA immunoassay method (Monobind, STATFAX-2100, USA).

Based on the results of the primary analysis, the individuals with high TSH and normal T4 and T3 were selected for the subclinical hypothyroidism group (group I).

In the next step, the healthy women who matched in number, age, and body mass index (BMI) with group I were selected for the control group. After receiving their consent, 5 ml of blood was collected from them, and the serum levels of TSH, T4, and T3 were measured using the same procedure. Finally, the serum level of selenium in both groups (I and II) was measured using the atomic absorption method (Thermo Jarrell Ash Spectrometer).

In summary, the method process is illustrated in Figure 1.

Statistical analysis

The statistical analysis was performed with SPSS statistical software version 21. All data were expressed as the mean \pm standard deviation (SD). A paired Student's t-test was used to analyze the results for significant differences. Pearson's correlation coefficients and logistic regression were used to analyze associations. P-values less than 0.05 were considered statistically significant.

Results

The information of the individuals who entered the study is presented in Table 1. Among the entire group, there were 41 (6.48%) females in the subclinical hypothyroidism group (high levels of TSH and normal T3 and T4).

Table 1. Phase 1 findings

Participant	Parameter	Value (mean \pm SD)
Total (550)	Age (years)	10.93 \pm 42.74
	TSH (mIU/ml)	4.3 \pm 2.81
	T4 ($\mu\text{g}/\text{dl}$)	8.42 \pm 3.96
	T3 (ng/ml)	1.65 \pm 0.37

SD = standard deviation; TSH = thyroid-stimulating hormone; T4= thyroxine; T3 = triiodothyronine

According to Table 2, there were no significant differences between the groups in terms of age and

Table 2. Descriptive statistics and clinical characteristics of the groups

Variables	Unit	Group I (n=41) (mean \pm SD)	Group II (n=41) (mean \pm SD)	p-value
Age	Year	9.41 \pm 39.29	9.18 \pm 38.91	NS
BMI	kg/m ²	25.3 \pm 2.1	24.9 \pm 1.3	NS
TSH	mIU/ml	2.02 \pm 7.57	1.54 \pm 2.14	S
T3	ng/ml	0.07 \pm 1.35	0.13 \pm 1.22	NS
T4	$\mu\text{g}/\text{dl}$	1.36 \pm 7.46	1.67 \pm 7.11	NS
Se	$\mu\text{g}/\text{l}$	11.33 \pm 72.92	9.21 \pm 86.48	S

S = significant; NS = non-significant; SD = standard deviation; BMI = body mass index; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4= thyroxine; Se = selenium

Table 3. Relationships between variables in the groups

		Age		BMI		TSH		T3		T4	
		patient	control	patient	control	patient	control	patient	control	patient	control
BMI	R	0.538	0.552								
	p-value	0.181	0.169								
TSH	R	0.498	0.421	0.161	0.212						
	p-value	0.143	0.104	0.513	0.172						
T3	R	0.207	0.218	0.162	0.198	0.235	0.212				
	p-value	0.166	0.156	0.043*	0.024*	0.009*	0.040*				
T4	R	0.228	0.246	0.171	0.243	0.420	0.473	0.192	0.093		
	p-value	0.138	0.107	0.755	0.821	0.251	0.265	0.615	0.548		
Se	R	0.248	0.826	0.095	0.142	0.078	0.228	0.298	0.303	0.152	0.131
	p-value	0.521	0.393	0.566	0.118	0.032*	0.191	0.019*	0.046*	0.707	0.840

BMI = body mass index; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4= thyroxine; Se = selenium; * = $P < 0.05$

BMI ($p > 0.05$). In addition, a significant difference was observed in the serum levels of TSH and Se in group I compared to the control group ($p < 0.05$).

Table 3 shows the correlation between the variables. There was a significant relationship between serum T3 and TSH levels and selenium levels in the groups. In group I, there was a correlation between TSH and Se ($p = 0.032$). There was a significant correlation between serum selenium level and subclinical hypothyroidism based on logistic regression analysis (Table 4).

Table 4. Logistic regression results showing the association between selenium and subclinical hypothyroidism (absence of subclinical hypothyroidism is the basis of comparison)

Variable	OR	95% CI for OR	p-value
Se	0.781	0.580-1.302	0.009

OR = odds ratio; CI = confidence interval; P-value < 0.05 is statistically significant. Se = selenium

Discussion

Thyroid gland disorders, second only to diabetes mellitus, are the most common disorders associated with endocrine glands. Hyperthyroidism and hypothyroidism are caused by elevated and decreased levels

of thyroid hormones, respectively. In the case of subclinical hypothyroidism, TSH levels are elevated while T4 and T3 levels remain normal¹. A study conducted by Negro *et al.* in 2008 examined a group of selenoproteins known as DIO enzymes, which play a crucial role in the conversion of T4 to T3 and the regulation of thyroid hormone metabolism. Surprisingly, the study found that selenium supplements could actually cause thyroid inflammation, despite the long-standing belief that selenium had a therapeutic effect on autoimmune thyroid diseases¹⁵.

Dharmesena *et al.* (2014) showed thyroid drugs plus selenium (during selenium deficiency) can be useful in the treatment of Graves' disease and autoimmune thyroiditis¹². There is a U-shaped relationship between selenium and disease, and either a deficiency or excess of it may lead to adverse outcomes. Hence, a balanced diet or supplementation with selenium can prevent thyroid disease and improve overall health. Based on the Mara Ventura *et al.* study (2016), selenium supplementation in patients with Hashimoto's thyroiditis and reducing its consumption in patients treated with levothyroxine may be beneficial¹⁰. Another study by Qian Wu *et al.* showed a correlation between the prevalence of thyroid diseases and soil selenium levels. They found that areas with sufficient levels of selenium in the soil had significantly lower rates of thyroid diseases, including hypothyroidism,

subclinical hypothyroidism, autoimmune thyroid diseases, and thyroid enlargement. The study also revealed that the decrease in selenium concentration in the soil was associated with an increase in the prevalence of thyroid diseases, suggesting that selenium intake can help reduce the occurrence of these diseases in areas with selenium deficiency¹⁶. There was no correlation between serum selenium levels and TSH in the study by Masanobu Kawai *et al.* (2018), but serum FT4 levels were increased in selenium deficiency and decreased by selenium supplementation¹⁷. In addition, in a study conducted by Ilenia Pirola (2020) regarding the use of selenium supplements in subclinical hypothyroid patients under the influence of autoimmune thyroiditis, the results showed the short-term use of selenomethionine supplements accompanied by normalization of thyroxine levels. They received 83 micrograms of selenomethionine per day orally in a softgel capsule for 4 months with water after meals. No other treatment was performed¹⁸. Similarly, the study by Kryczyk-Kozioł *et al.* aimed to explore the positive effects of selenium supplementation in women diagnosed with Hashimoto's thyroiditis who had low selenium levels. The findings indicated that selenium supplementation significantly reduced the levels of antithyroid peroxidase¹⁹. Furthermore, Keilla Mayumi *et al.* reported that selenium supplementation is essential to prevent the aggravation of hypothyroidism²⁰. Beckett *et al.* showed that selenium deficiency caused a significant increase in the activity of the liver cytosolic malic enzyme and mitochondrial alpha-glycerophosphate dehydrogenase (GPD). Hormone concentration in hypothyroidism tissue caused by propylthiouracil has caused a significant decrease in the activity of the malic enzyme and GPD²¹. In conclusion, our study found that the prevalence of subclinical hypothyroidism in the study area (Bojnurd, North Khorasan, Iran) was approximately 6.48%. Additionally, a significant relationship was observed between serum selenium levels and subclinical hypothyroidism. Therefore, conducting more comprehensive studies to investigate selenium status in the region is recommended.

Authors Contribution

Kimiya Hadavi and Ali Esmaeili both contributed equally to this work and are considered co-first authors

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Sažetak

PREVALENCIJA SUBKLINIČKE HIPOTIREOZE I RAZINE SELENA U ŽENA SJEVERNOG HORASANA U IRANU: PRESJEČNO ISTRAŽIVANJE

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Osobe sa subkličičkom hipotireozom imaju povećan rizik od razvoja kliničke hipotireoze. Štitnjača, koja ima najveću koncentraciju selena po gramu tkiva među odraslima, igra ključnu ulogu u metabolizmu hormona štitnjače. Ovo je istraživanje imalo za cilj istražiti prevalenciju subkličičke hipotireoze u pokrajini Sjeverni Horasan u Iranu i procijeniti razinu selena u serumu u pogodehkih pojedinaca. Proveli smo prospektivnu studiju koja je uključivala 550 žena u dobi od 20 do 55 godina. Uzorci seruma prikupljeni su od pojedinaca na temelju kriterija uključivanja i isključivanja studije. Mjerali smo serumske razine stimulirajućeg hormona štitnjače (TSH), tiroksina (T4) i trijodtironina (T3). Nakon toga, pojedinci s visokim TSH, ali normalnim razinama T4 i T3 odabrani su za daljnju analizu (skupina I). Izmjerene su serumske razine TSH, T4, T3 (pomoću ELISA metode) i selena (metodom atomske apsorpcije) i uspoređene s onima kontrolne skupine koja se sastojala od zdravih žena koje su po broju, dobi i indeksu tjelesne mase odgovarale skupini I. Ukupna prevalencija subkličičke hipotireoze u ispitivanoj populaciji bila je 6.48%. Uočene su značajne razlike u serumskim razinama TSH i selena između skupine sa subkličičkom hipotireozom i kontrolne skupine. Nadalje, pozitivna korelacija između TSH i razine selena utvrđena je isključivo unutar skupine subkličičke hipotireoze. Pojava subkličičke hipotireoze bila je u pozitivnoj korelaciji s razinama selena u serumu.

Ključne riječi: *Selen; Hormoni štitnjače; Subkličička hipotireoza*